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We Claim:

1. A method for selecting a combination of therapeutic agents for treatment of a disease caused by a deranged cell signaling pathway or cell signaling pathway network that leads to an aberrant cellular response, comprising:

5 measuring activity states for a plurality of different signaling proteins extracted from a diseased cell, where the signaling proteins are members of one or more signaling pathways or networks;

determining whether the activity states measured for the plurality of signaling proteins extracted from the diseased cell are different than activity states measured for
10 corresponding signaling proteins from a reference cell to detect differences between the activity states of individual signaling proteins from the diseased cell and the activity states of the corresponding individual signaling proteins from the reference cell; and

selecting a combination of at least two different therapeutic agents, wherein the therapeutic agents are selected to target two or more different members of a protein
15 signaling pathway or network comprising an individual signaling protein for which a difference in activity state was detected between the diseased cell and the reference cell, wherein the agents reduce the difference in the activity state that was detected.

2. The method of claim 1, wherein the combination of therapeutic agents
20 provides a synergistic improvement in efficacy of treatment of the aberrant cellular response when compared the combined efficacies of the agents administered alone at the same dose.

3. The method of claim 1, wherein the diseased cell is obtained from tissue
25 of a subject, the method further comprising isolating the diseased cell from the tissue of the subject.

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4. The method of claim 3, wherein isolating the diseased cell comprises microdissection of the diseased cell from the tissue.

5 5. The method of claim 4, wherein microdissection comprises laser capture microdissection.

6. The method of claim 3, wherein isolating the diseased cell comprises isolating the diseased cell by fluorescence activated cell sorting.

10 7. The method of claim 1, further comprising extracting the plurality of different signaling proteins from a cell sample comprising the diseased cell.

8. The method of claim 7, wherein the cell sample is a sample of cells obtained by microdissection.

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9. The method of claim 8, wherein the cell sample is a sample of cells obtained by laser capture microdissection.

10 10. The method of claim 1, wherein measuring the activity states of the plurality of signaling proteins comprises measuring the activity states using protein microarray analysis, immunohistochemistry, antibody microarray analysis, or bead capture.

11. The method of claim 10, wherein the protein microarray analysis
25 comprises reverse phase protein microarray analysis.

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12. The method of claim 11, wherein the reverse phase protein microarray analysis comprises microarray analysis of phosphorylated signaling proteins using antibodies that specifically bind to a particular phosphorylated signaling protein.

5 13. The method of claim 12, wherein the microarray analysis comprises comprising microarray analysis of total amounts of signaling proteins using antibodies that specifically bind to particular signaling proteins regardless of their phosphorylation state, and the activity state of the signaling protein is determined as a ratio of the phosphorylated signaling protein to the total amount of the signaling protein.

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14. The method of claim 1, wherein the reference cell is a normal cell, a cell before or after a treatment, or a cell before or after a disease or a stage of disease.

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15. The method of claim 14, wherein the reference cell is a normal cell.

16. The method of claim 14, wherein the reference cell comprises a cell that has not been treated with a therapeutic agent.

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17. The method of claim 1, wherein the diseased cell and the reference cell are obtained from the same subject.

18. The method of claim 1, wherein the reference cell is obtained from one subject and the diseased cell is obtained from another subject.

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19. The method of claim 1, wherein one or both of the reference cell and the diseased cell are cultured cells.

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20. The method of claim 1, further comprising administering the combination to a subject from which the diseased cell was obtained.

21. The method of claim 1, wherein the aberrant cellular response comprises
5 abnormal growth, apoptosis, cytoskeletal remodeling, survival, receptor localization and distribution, gene transcription, motility, differentiation, proliferation, or angiogenesis.

22. The method of claim 1, wherein the measured activity states of the
10 signaling protein comprises one or more of a protein-protein interaction, a post-translational modification, a protein cleavage, a translocation to an organelle or compartment, an ion channel activation, a concentration of a soluble mediator that is a product or a substrate of the protein, a protein-nucleic acid interaction, a protein-lipid interaction, or a protein-carbohydrate interaction.

15 23. The method of claim 22, wherein the post-translational modification comprises phosphorylation, farnesylation, myristylation acetylation or ubiquitination.

24. The method of claim 1, wherein the combination is selected based on
prior success in a subject having a same difference in activity state for one or more
20 individual signaling proteins as is determined in a subject from which the diseased cell was obtained.

25. The method of claim 1, wherein determining differences between the activity states of the plurality of signaling proteins between the diseased cell and the
25 reference cell comprises pattern recognition.

26. The method of claim 1, wherein the combination of therapeutic agents comprises two or more of drugs that separately target a combination of EGFr

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dimerization, EGFr phosphorylation, AKT phosphorylation, non-voltage gated calcium ion channels, cyclooxygenase-1, cyclooxygenase-2, MEK-1, NFkB/IkB, and P38.

27. The method of claim 1, wherein the combination prevents shunting to or
5 around a signaling pathway.

28. The method of claim 27, wherein the combination includes a drug that inhibits MEK phosphorylation of ERK kinase, and shunting occurs via activation and phosphorylation of CREB.
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29. The method of claim 1, wherein the combination comprises a prostaglandin pathway effector and a non-voltage gated calcium influx channel effector.

30. The method of claim 1, wherein the combination comprises CaI and a
15 specific COX-2 inhibitor.

31. The method of claim 30, wherein the specific COX-2 inhibitor comprises Rofecoxib, Celecoxib or LM-1685.

20 32. The method of claim 1, wherein the combination comprises an AKT kinase inhibitor and either an EGFR dimerization inhibitor or an EGF kinase inhibitor.

33. The method of claim 32, wherein the EGF dimerization inhibitor comprises hereceptin and the EGF kinase inhibitor comprises IRESSA.
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34. The method of claim 1, wherein the combination comprises a PKCalpha agonist resulting in phosphorylation and activation of PKCalpha.

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35. The method of claim 32, wherein the combination comprises an AKT kinase inhibitor and herceptin.

36. The method of claim 1, wherein the disease comprises a
5 neurodegenerative disease, memory loss or cancer.

37. The method of claim 35, wherein the disease comprises breast cancer or colon cancer.

10 38. The method of claim 1, wherein one or more of the signaling proteins in the plurality of different signaling proteins are members of an integrin pathway, a focal adhesion signaling pathway, an Akt signaling pathway, an IL-6R pathway, a growth factor pathway, a chemokine receptor signal pathway, a cell-cycle signaling pathway, a stress signal pathway, an apoptosis signaling pathway, a Tau/beta signaling pathway, a
15 pro-inflammatory pathway, a differentiation signaling pathway, a T-cell receptor pathway, a death-receptor signaling pathway, a survival signaling pathway, a MAPK signaling pathway, a p38 MAPK signaling pathway, a G-coupled Receptor signaling pathway, a SAPK/JNK signaling pathway, an insulin receptor signaling pathway, a Wnt signaling pathway, a c-Kit pathway, a c-kit signaling pathway, a B-cell antigen
20 signaling pathway, or a Jak/Stat signaling pathway.

39. The method of claim 1, wherein the activity state is phosphorylation of the signaling protein and measuring comprises determining a ratio of the amount of phosphorylated signaling protein to the total amount of signaling protein.

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40. The method of claim 1 further comprising repeating the steps of claim 1 for a second diseased cell obtained from a subject or a cell culture during or following administration of the combination the subject or the cell culture and combining at least

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one additional therapeutic agent with the combination to make a second combination, wherein the at least one additional therapeutic agent in the second combination reduces a difference in the activity state that was detected by repeating the steps of claim 1.

5 41. The method of claim 1, wherein the difference in activity states detected is an increase in the activity state of an individual signaling protein from the diseased cell in comparison to the same signaling protein in the reference cell, and the therapeutic agents are selected to counteract the increase in the activity state of the individual signaling protein from the diseased cell.

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 42. The method of claim 41, wherein the increase in activity state of the individual signaling protein from the diseased cell is an increase in phosphorylation and the therapeutic agents are selected to counteract the increase in phosphorylation of the individual signaling protein from the diseased cell.

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 43. The method of claim 1, wherein the difference in activity-states detected is a decrease in the activity state of an individual signaling protein from the diseased cell in comparison to the same signaling protein in the reference cell, and the therapeutic agents are selected to counteract the decrease in the activity state of the
20 individual signaling protein from the diseased cell.

 44. The method of claim 43, wherein the decrease in activity state of the individual signaling protein from the diseased cell is a decrease in phosphorylation and the therapeutic agents are selected to counteract the decrease in phosphorylation of the
25 individual signaling protein from the diseased cell.

 45. The method of claim 1, wherein the differences detected are a concordant increase in phosphorylation of a protein belonging to the c-kit family of

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proteins and an estrogen receptor in the diseased cell relative to the reference cell, and the combination comprises an aromatase inhibitor and STI-572.

46. A method for treatment of a subject having a disease caused by a
5 deranged signaling pathway or network leading to an aberrant cellular response,
comprising:
- obtaining a sample comprising a diseased cell from the subject;
 - isolating the diseased cell from the sample;
 - extracting proteins from the diseased cell;
 - 10 measuring an activity state of a signaling protein extracted from the diseased
cell;
 - comparing the activity state of the signaling protein extracted from the diseased
cell to an activity state measured for the signaling protein extracted from a reference
cell to determine a difference in the activity states of the signaling protein between the
15 diseased cell and the reference cell that indicates the signaling pathway of which the
signaling protein is a member is a deranged signaling pathway or network;
 - selecting a combination of at least two therapeutic agents for administration to
the subject, the therapeutic agents selected to target two or more members of the
deranged protein signaling pathway or network, wherein the agents reduce the
20 difference in activity state that determined; and
 - administering the combination to the subject.

47. A method for screening combinations of drugs for treatment of a
pathological condition, comprising:
- 25 selecting a combination of drugs targeting two or more nodes in a protein
signaling pathway or network of a diseased cell exhibiting the pathological condition,
the pathway or network having an aberrant pattern of activity states at one or more

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nodes in comparison to a pattern of activity states at the one or more nodes for a normal cell;

treating the diseased cell with the selected combination of drugs; and

examining the pattern of activity states exhibited by the diseased cell following

5 treatment with the combination to determine whether the combination of drugs produces a pattern of activity states in the diseased cell that is more like the pattern of activity states for the normal cell, where a pattern that is more like the pattern for the normal cell identifies the combination as a candidate for treatment of the pathological condition.

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48. The method of claim 47 further comprising treating the diseased cell with each of the drugs in the combination alone and at substantially the same dose as in the combination, examining the activity states of the one or more nodes after treatment with each of the drugs separately, and comparing the activity states produced by the
15 combination to the activity states produced by the drugs alone to determine if the combination synergistically alters the pattern of activity states toward the pattern for the reference cell.

49. The method of claim 48, wherein the patterns of activity states are
20 determined and compared using pattern recognition.

50. The method of claim 47, wherein the pattern of activity states is a pattern of phosphorylation.